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A Novel Synthesis of 2,3-Dimethoxy-5-methyl-*p*-benzoquinone[1]

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2,3-Dimethoxy-5-methyl-*p*-benzoquinone (**3**), an important intermediate in the synthesis of ubiquinones (**1**), was synthesized from 3,4,5-trimethoxysalicylic acid (**6**) or 2,3,4-trimethoxybenzaldehyde (**9**). **6** was reduced *via* the ethoxycarbonyl derivative (**7**) to 6-methyl-2,3,4-trimethoxyphenol (**8**) with sodium borohydride, and then **8** was oxidized to **3** in high yield with ferric chloride. On the other hand, 2,3,4-trimethoxyphenol (**10**) was obtained from **9** by the Baeyer–Villiger reaction or treatment with hydrogen peroxide under acidic or basic conditions, and then converted into **8** by reductive methylation. Sodium borohydride reduction of the Mannich base (**11**) of **10** also gave **8**.

Keywords——2,3-dimethoxy-5-methyl-*p*-benzoquinone; ubiquinones; 3,4,5-trimethoxysalicylic acid; 2,3,4-trimethoxybenzaldehyde; 6-methyl-2,3,4-trimethoxyphenol; 2,3,4-trimethoxyphenol; 6-(N,N-dimethylamino)methyl-2,3,4-trimethoxyphenol; sodium borohydride reduction; reductive methylation

Ubiquinones (**1**) are generally synthesized by the condensation of 2,3-dimethoxy-5-methylhydroquinone (**2**) with polyprenyl alcohol, followed by oxidation of the condensation product,[3] and **2** is synthesized by reduction of 2,3-dimethoxy-5-methyl-*p*-benzoquinone (**3**). Therefore, **3** is a very important intermediate in the synthesis of **1**.

Many methods for the synthesis of **3** from vanilin[4] and gallic acid[5] are known, but are

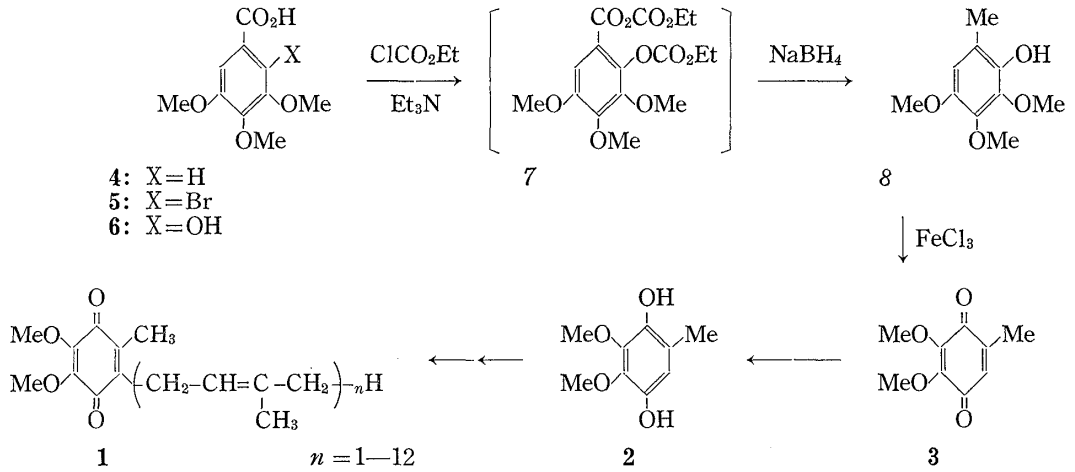

Chart 1

1) A part of this work was presented at the 98 th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 1978.
2) Location: *Koishikawa 4-6-10, Bunkyo-ku, Tokyo 112, Japan.*
3) U. Gloor, O. Isler, R.A. Morton, R. Ruegg, and O. Wiss, *Helv. Chem. Acta*, **41**, 2357 (1958); C.H. Shunk, B.O. Linn, E.L. Wong, P.E. Wittreich, F.M. Robison, and K. Folkers, *J. Am. Chem. Soc.*, **80**, 4753 (1958).
4) W.K. Anslow, J.N. Ashley, and H. Raistrick, *J. Chem. Soc.*, **1938**, 439; M. Shimizu and K. Koshi, *Chem. Pharm. Bull.*, **11**, 404 (1963); L. Blaha and J. Weichet, *Collect. Czech. Chem. Commun.*, **30**, 2068 (1965).
5) F. Hoffmann-La Roche Co., Brit. Patent 889704 (1962) [*C.A.*, **57**, 4596 (1962)]; E.A. Oblnikova, O.I. Volkova, and G.I. Samokhvalov, *Zn. Obshch. Khim*, **38**, 459 (1968).

complex, multi-step processes. The present paper describes a novel synthesis of **3** from 3,4,5-trimethoxysalicylic acid (**6**) or 2,3,4-trimethoxybenzaldehyde (**9**).

From 3,4,5-Trimethoxysalicylic Acid (6)

According to the method of Mayer and Fikentscher,[6] **6** was synthesized by the bromination of **4** with bromine, followed by hydrolysis of the resulting 2-bromo-3,4,5-trimethoxybenzoic acid (**5**) with the aid of cupric ions in an aqueous basic medium. In the previous paper[7] we reported that the ethoxycarbonyl derivative of salicylic acid was reduced by sodium borohydride to give *o*-cresol. Thus, the ethoxycarbonyl derivative (**7**) was prepared from **6** and 2 equivalents of ethyl chloroformate in the presence of 2 equivalents of triethylamine in tetrahydrofuran, and was added to an aqueous solution of sodium borohydride. 6-Methyl-2,3,4-trimethoxyphenol (**8**) was obtained in 71.7% yield. In this process it was difficult to obtain pure **5** and **6**, but when this process was carried out without purification of **5** and **6**, **8** was obtained in 52.0% overall yield from **4**. **8** was oxidized with ferric chloride in benzene–water to give **3** in 95.7% yield.

From 2,3,4-Trimethoxybenzaldehyde (9)

The transformation of **9** to 2,3,4-trimethoxyphenol (**10**) was successfully achieved by means of the Baeyer-Villiger reaction. When **9** was treated with peracetic acid in the presence of sulfuric acid in methanol, **10** was obtained in 95.4% yield. When hydrogen peroxide was used in place of peracetic acid, the yield of **10** was 88.7%. As stated above, under acidic conditions **10** was obtained in good yield, but when **9** was treated with hydrogen peroxide under basic conditions, **10** was obtained in low yield (38.9%). The phenol (**10**) was then subjected to reductive methylation in methyl borate in the presence of 10% Pd–C, paraformaldehyde, boric acid and acetic acid under a pressure of 60 atm of hydrogen at 190°. **8** was obtained in quantitative yield. On the other hand, **10** was transformed to the Mannich base, 6-(N,N-dimethylamino)methyl-2,3,4-trimethoxyphenol (**11**) according to Sato's procedure.[8] Hutchins *et al.*[9] reported that sodium borohydride in dimethylsulfoxide reduced the Mannich base, 1-(N,N-dimethylamino)methyl-2-naphthol, to 1-methyl-2-naphthol in high yield (80%). However, **11** gave **8** in low yield (38.7%) with sodium borohydride in dimethylsulfoxide at 100—110°.

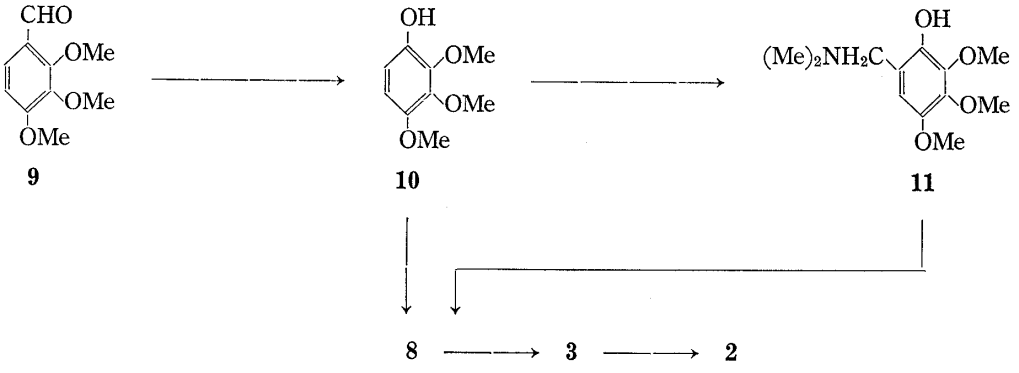

Chart 2

We thus established two simple and high yield method to obtain **3**, involving sodium borohydride reduction of the ethoxycarbonyl derivative (**7**) of **6** and reductive methylation of **10**.

6) W. Mayer and R. Fikentscher, *Chem. Ber.*, **89**, 511 (1956).
7) N. Minami and S. Kijima, *Chem. Pharm. Bull.*, **27**, 816 (1979).
8) K. Sato, S. Inoue, and H. Sato, *Bull. Chem. Soc. Jpn.*, **45**, 3455 (1972).
9) R.O. Hutchins, D. Hoke, J. Keogh, and D. Kobarski, *Tetrahedron Lett.*, **1969**, 3495.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were measured with a Hitachi 215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were measured with a JEOL PS-100 spectrometer using TMS as an internal standard.

6-Methyl-2,3,4-trimethoxyphenol (8) from 3,4,5-Trimethoxysalicylic Acid (6)——Ethyl chloroformate (19.5 g, 0.18 mol) was added to a solution of **6** (18.3 g, 0.08 mol)and triethylamine (18.2 g, 0.18 mol) in tetrahydrofuran (200 ml) at 0—5° over a period of 1 hr. After standing for 45 min at the same temperature, the white precipitate (triethylammonium chloride) was filtered off, washed with tetrahydrofuran (100 ml), and the combined filtrate was added to a solution of sodium borohydride (12.1 g, 0.32 mol) in water (250 ml) with stirring at 5—15° over a period of 1 hr. When the addition was complete, the reaction mixture was stirred at room temperature for 3 hr, then diluted with water, made acidic with dil. HCl and extracted with benzene (500 ml). The benzene layer was extracted with 5% aqueous NaOH (250 ml). The aqueous layer was neutralized with dil. HCl and extracted with benzene (500 ml), which was then washed with water and 5% aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the benzene *in vacuo* gave **8** (11.4 g, 71.7%). IR $\nu_{max}^{liq.}$ cm^{-1}: 3450 (–OH). NMR ($CDCl_3$) δ: 2.15 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.80 (1H, broad, OH), 6.40 (1H, s, aromatic H). This was used in the next step without further purification.

2,3-Dimethoxy-5-methyl-*p*-benzoquinone (3)——A solution of **8** (10.0 g, 0.05 mol) in benzene (200 ml) was added to a solution of ferric chloride·6 H_2O (50 g) in water at room temperature over a period of 30 min. After stirring for 3 hr at room temperature, the benzene layer was separated, and the water layer was extracted with benzene (300 ml). The combined benzene layer was washed with water and dried over $MgSO_4$. Removal of the benzene gave **3** (8.8 g, 95.7%). mp 58—60° (from benzene–*n*-hexane) (reported,[8] mp 58—59°). IR ν_{max}^{Nujol} cm^{-1}: 1650, 1600. NMR ($CDCl_3$) δ: 2.05 (3H, d, CH_3), 4.00 (6H, s, $2\times OCH_3$), 6.40 (1H, q, =CH).

2,3,4-Trimethoxyphenol (10) from 2,3,4-Trimethoxybenzaldehyde (9)——a) Peracetic Acid in the Presence of Sulfuric Acid: 40% Peracetic acid (42 ml, 0.22 mol) was added to a solution of **9** (39.2 g, 0.2 mol) and conc. sulfuric acid (8 ml) in methanol (200 ml)–water (100 ml) over a period of 30 min at 15—35°. After stirring for 2 hr at 20°, the reaction mixture was diluted with water. Excess peracetic acid was decomposed with sodium thiosulfate, and the reaction mixture was extracted with ether (500 ml). The ether layer was washed with 5% aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the ether *in vacuo* gave **10** (35.1 g, 95.4%). IR $\nu_{max}^{liq.}$ cm^{-1}: 3440. NMR ($CDCl_3$) δ: 3.70 (3H, s, OCH_3), 3.80 (6H, s, $2\times OCH_3$), 5.90 (1H, broad, OH), 6.50 (2H, s, aromatic H). This was used in the next step without further purification.

b) Hydrogen Peroxide in the Presence of Sulfuric Acid: 35% H_2O_2 (6.4 ml) was added to a solution of **9** (5.0 g, 0.026 mol), acetic acid (9 ml) and sulfuric acid (1 ml) in methanol (40 ml)–water (10 ml) over a period of 15 min at 18°. After standing overnight, work-up was carried out in a manner similar to that described in a). **10** was obtained in 87.7% yield (4.2 g). Its IR spectrum was identical with that of the sample obtained by method a).

c) Hydrogen Peroxide in the Presence of Sodium Hydroxide: 35% H_2O_2 (41 ml) was added to a solution of **9** (11.8 g, 0.06 mol) and sodium hydroxide (2.4 g) in ethanol (100 ml)–water (30 ml) over a period of 30 min at 30°. After stirring for 3 hr at 40—45°, the reaction mixture was made acidic with dil. HCl and work-up was carried out in a manner similar to that described in a). **10** was obtained in 38.9% yield (4.3 g). Its IR spectrum was identical with that of the sample obtained by method a).

6-Methyl-2,3,4-trimethoxyphenol (8) from 2,3,4-Trimethoxyphenol (10)——A mixture of **10** (9.2 g, 0.05 mol), paraformaldehyde (5 g), boric acid (5 g) and acetic acid (0.5 ml) in methyl borate (50 ml) was put into an autoclave and hydrogenated at 190° for 4 hr in the presence of 10% Pd–C (1 g). The filtrate was diluted with benzene (250 ml), washed with water, and extracted with 5% aqueous NaOH (200 ml). The aqueous layer was neutralized with dil. HCl, and extracted with benzene (250 ml). The benzene layer was washed with water and 5% aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the benzene *in vacuo* gave **8** quantitatively (9.8 g). Its IR spectrum was identical with that of the sample obtained from **6**.

6-Methyl-2,3,4-trimethoxyphenol (8) from 6-(N,N-Dimethylamino)methyl-2,3,4-trimethoxyphenol (11)—A solution of **11** (729 mg, 3 mmol) in dimethylsulfoxide (5 ml) was added to a solution of sodium borohydride (227 mg, 6 mmol) in dimethylsulfoxide (10 ml) and the mixture was stirred for 3 hr at 100—110°. After acidification with dil. HCl under ice-cooling, the mixture was extracted with ether. The ether layer was washed with water, and dried over $MgSO_4$. The extracts were chromatographed on silica gel (60—80 mesh) using *n*-hexane–ether as an eluent. **8** was obtained in 38.7% yield (230 mg). Its IR spectrum was identical with that of the sample obtained from **6**.